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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,725	11/16/2000	Ying Luo	RIGL-008CIP	6653

24353 7590 08/10/2005

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ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,725	LUO ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *April 25, 2005, May 13, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *26,27,29,30 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) *26,27,29,30 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/1/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-02

1. The Amendment filed April 25, 2005 in response to the Office Action of January 24, 2005 is acknowledged and has been entered. The Supplemental Response filed May 13, 2005 in response to the Office Action of January 24, 2005 is acknowledged and has been entered. Previously pending claims 27 and 30 have been amended. Claims 26-27, 29-30 and 32 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC 112

3. Claims 26-27, 29-30, 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to a recombinant ING2 protein encoded by the contiguous polynucleotide sequence of nucleotides 120-845 of the nucleic acid set forth in SEQ ID NO:7,SEQ ID NO:8, a recombinant polypeptide having at least 95% identity to SEQ ID NO:8.

The specification teaches that ING2 protein, of which SEQ ID NO:8 is an isoform, is useful for screening for bioactive agents capable of interfering with the binding of a cell cycle protein and the IAPs, screening for bioactive agents that modulate the activity of a cell cycle protein (p. 3), the specification teaches its use in an assay to screen for a bioactive agent capable of modulating apoptosis, its use in an assay to screen for a bioactive agent capable of modulating the cell cycle (p. 4), the specification points to the similarity of ING2 to proteins belonging to a

family of tumor suppressors in particular ING1 (p. 6, lines 30-35), inferring perhaps that ING2 and by extension, SEQ ID NO:8 would be useful as a tumor suppressor, the specification teaches that ING2 is a cell cycle protein and that ING2 activates p53 binding site controlled promoters in the presence or absence of p53 and acts synergistically with p53 to stimulate induction (p. 7, lines 8-10). The specification discloses a graph depicting p53 activation by ING2 wherein it is disclosed that ING2b and 2c apparently activate p53 and that in combination with p53 the activation is potentiated (see Figure 12). It is noted that although Applicant suggests in arguments that the induction of transcription by SEQ ID NO:8 in the absence of p53 is made clear by Figure 12, since there is no nexus provided in the specification between SEQ ID NO:8 and ING2b or 2c, it is not possible to evaluate Applicant's argument. Further, the specification does not disclose any teaching of which system was used to determined that ING2 activates said promoter or is synergistic with p53. In particular, it is well known in the art that *in vitro* transfection of cells with constructs encoding novel polypeptides lead to activity which one would not normally find in those cells. It is not clear whether the information taught in the specification was drawn from *in vitro* experiments with transfected cells, whether p53 and SEQ ID NO:8 were incubated with cells and that led to the disclosed activation, no teaching of which promoter is activated, in which tissue it is found, no teaching of what effect this activation had on the cell or on any system. Thus, it is not possible for the skilled practioner to evaluate the statements in the specification and one would not be able to predict that the invention will function as contemplated.

The specification suggests the use of ING2 and by extension SEQ ID NO:8 in inducing or preventing cell proliferation in cells (p43), its use in the diagnosis,

treatment, prevention of cell cycle associated disorders, preferably cancer (p. 44). It is noted that there is no teaching or evidence in the specification or in the art of record that SEQ ID NO:8 proteins are in any way associated with the cell cycle or with apoptosis. There is no disclosure of why Applicants think that SEQ ID NO:8 binds to an IAP. In addition, the specification teaches that SEQ ID NO:8 is useful in the study or treatment of conditions which are mediated by the cell cycle proteins, i.e. to diagnose, treat or prevent cell cycle associated disorders and these disorders include conditions involving both insufficient or excessive cell proliferation and preferably cancer (p. 44). Finally, the specification teaches general methods of diagnosing cell cycle related conditions including assaying for differences in amount or specific activity of a cell cycle protein (p. 44-45), assaying the levels of cell cycle protein genes (p. 45-48).

One cannot extrapolate the teaching of the specification to the enablement of the claims because there is no teaching either in the specification or the art of record which IAP SEQ ID NO:8 binds, or whether SEQ ID NO:8 binds to any IAP particular IAP, thus one could not predict that the claimed polypeptide could be used for screening for bioactive agents capable of interfering with the binding of SEQ ID NO:8 and IAPs. Further, although the specification suggests that ING2 proteins are useful for screening for bioactive agents that modulate the activity of a cell cycle protein and Figure 12 might suggest that ING2b and ING2c modulate activation of p53 (a cell cycle protein sometimes involved with apoptosis), there is no nexus found, either in the specification or the art of record that either ING2b or ING2c are in fact SEQ ID NO:8. Although Applicant has submitted Shiseki et al (Can. Res., 2003, 63:2373-2378) which teaches that a polypeptide which Applicant argues has 100% identity to SEQ ID NO:8, except for 13 amino acids at its N-

terminus, in conjunction with p53 activates the known p53-responsive p21/waf-1 promoter (apparently by binding to p53) it cannot be predicted that the function of SEQ ID NO:8 would be the same as that of the polypeptide of Shiseki et al because although the specification teaches that ING2 polypeptides activate p53 binding site controlled promoters in the presence or absence of p53, the polypeptide of Shiseki et al does not activate the p53-responsive p21/waf-1 promoter in the absence of p53 (p. 2377, col 1). Thus it is clear that the 13 amino acid difference of the polypeptide of Shiseki et al from the instantly claimed invention has a profound effect on the Shiseki et al polypeptide's ability to function as that which is disclosed by the instant specification. Further, given that Shiseki et al suggest that the effects of the polypeptide on activation of the promoter is due to the physical interaction of the polypeptide with p53, which could regulate p53 by recruiting cofactors which enhance acetylation of p53, given the teachings of record drawn to the unpredictability of protein chemistry, the teachings of Bowie et al, Bork, Burgess et al, Lazar et al, all of record (see the Action mailed August 8, 2003, pages 6-8) it could not be predicted, based on the identity of the polypeptide of Shiseki et al and SEQ ID NO:8 that SEQ ID NO:8 would function in the same manner as the polypeptide of Shiseki et al, that is to increase the activity of a promoter having a p53 binding site, particularly in view of the clear differences in promoter binding of the two polypeptide. Given the above, although Applicant argues strongly that because the polypeptide of Shiseki et al has identity to amino acids 30-229 of SEQ ID NO:8, and that one would reasonably conclude that SEQ ID NO:8 increases the activity of promoters having p53 binding sites and as such may be used to modulate apoptosis of a cell, it is clear that for the reasons set forth above that it could not be predicted that the invention would function as suggested

(that is to screen for a bioactive agent capable of modulating apoptosis, capable of modulating the cell cycle, that SEQ ID NO:8 is a cell cycle protein) in the absence of further guidance and one would not know how to use the claimed invention to screen for a bioactive agent capable of modulating apoptosis, capable of modulating the cell cycle, that SEQ ID NO:8 is a cell cycle protein based only on the information in the specification and in the art of record.

Further, although Applicant clearly suggests that the claimed polypeptide activates p53 binding site controlled promoters in the presence or absence of p53 and even if it were to be found that Figure 12 does demonstrate that SEQ ID NO:8 activates a p53 binding site controlled promoter, as set forth above, there is no guidance in either the specification or the art of record that discloses which p53 binding site controlled promoter SEQ ID NO:8 activates. In particular, Szak et al (Mol. Cel. Biol., 21:2001, 3375-3386) specifically teach the complexity of the p53 cell cycle protein cascade wherein p53, by its ability to bind DNA in a sequence-specific manner, coordinates transitions between cell cycle phases, stimulating growth arrest and also initiates apoptosis by transactivation of genes (p. 3375, cols 1 and 2). The reference teaches that there is an ever-increasing number of p53 downstream targets being identified. The reference analyzed the kinetics of p53 binding to p53 consensus binding sites in select target gene promoters including p21/waf1, MDM2 and PIG3 wherein it was found that p53 has differential affinity for response elements in down-stream promoters (p.3380, col 2 to 3381). Thus given the differential binding of the p53 to its response elements in promoters which results in differential activation of those promoters, it would also be expected that there would be a differential binding of SEQ ID NO:8 to p53 binding site controlled promoters, therefore a differential activation. The diversity and

complexity in p53 response elements is clearly well known in the art and even if it were to be determined that SEQ ID NO:8 binds to and activates a p53 binding site controlled promoter the specification provides no guidance as to which promoter that may be or what the effect that that activation might be. Given the number of genes controlled by p53, given the clear complexity of p53 binding site controlled promoters it could not be predicted from the information in the specification or from the art of record which one or ones of those promoters would be activated by SEQ ID NO:8, in which tissue or cell type they reside, or what the effect of that activation might be. Thus the skilled artisan is left with random experimentation to determine which of the known and unknown promoters controlled by p53 SEQ ID NO:8 activates. Applicant is reminded that in order to satisfy the requirements of 35 USC 112, first paragraph, it is required that the specification teach how to make and use the claimed invention. Applicant is reminded that the screening assays taught in the specification do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. Given the lack of information as to which promoter(s) are activated or which in which tissue they are found and what the effect of that activation might be, one could not predict how to use the claimed invention.

The specification further suggests that ING2 proteins are useful for screening for bioactive agents capable of modulating apoptosis, however, neither the specification nor the art of record discloses that SEQ ID NO:8 is in any way associated with apoptosis. In particular, even if it were to be found that SEQ ID NO:8 activates p53, as set forth above, p53 activity is not limited to apoptosis

processes but is also involved in cell cycle arrest processes and it could not be predicted from the information in the specification whether SEQ ID NO:8 activation is associated with apoptosis or cell cycle arrest. The specification clearly teaches the novelty of the claimed invention. It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

The specification states that ING2, and by extension SEQ ID NO:8, is a cell cycle protein/tumor suppressor and appears to infer that ING2, and again by extension SEQ ID NO:8, could be used as a tumor suppressor based on its identity to ING1. Although a review of the literature has revealed homology of SEQ ID NO:8 to ING1, that homology is very limited. SEQ ID NO:8 shares 36.5% local similarity with 33.6% of the ING1 polypeptide, and in fact has only a 12.3%

identity with the ING1 polypeptide. Thus the apparent designation of SEQ ID NO:8 as a cell cycle protein is based on overall homology of SEQ ID NO:8 to ING1 of 12.3%. Further, although the identity is 12.3%, the lack of identity of SEQ ID NO:8 to ING1 is 87.7%. Given that the specification teaches that cell cycle proteins can be identified by substantial amino acid sequence identity or similarity (greater than 75% to about 98% identity) to the sequence as shown in Figure 8, SEQ ID NO:8 (p. 7, lines 31-35), it would appear that, by the teaching of the specification, the ING1 gene product is neither a cell cycle protein nor a tumor suppressor. If the ING1 gene product is not a cell cycle protein/tumor suppressor and the designation of the ING2 isoform as a cell cycle protein/tumor suppressor is based on homology to the ING1 gene product, then SEQ ID NO:8 could not be either a cell cycle protein or a tumor suppressor as defined by the specification. Given the above, one could not predict how to use the claimed invention.

The specification further teaches that SEQ ID NO:8 is useful in inducing or preventing cell proliferation in the treatment of conditions which are mediated by the cell cycle proteins, i.e. to diagnose, treat or prevent cell cycle associated disorders and that these conditions involve both insufficient or excessive cell proliferation and these disorders and conditions are preferably cancer. However, neither the specification nor the art of record provides a nexus between SEQ ID NO:8 and any cell cycle associated disorder. There is no teaching of any changes in SEQ ID NO:8 that are associated with any disorder or disease. There is no teaching of the overexpression, underexpression or mutation of SEQ ID NO:8 that could be linked to the diagnosis of any disease or which would lead to a reasonable expectation of success in the targeting of SEQ ID NO:8 for the treatment of any disease. Again, as set forth above, it is noted that MPEP 2164.03 teaches that "the

amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

4. Claims 27, 30 and 32 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of "a recombinant ING2 protein, comprising an amino acid sequence having at least 95% identity to the contiguous sequence set forth in SEQ ID NO:8

wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell" has no clear support in the specification and the claims as originally filed. Applicant cites support for the newly claimed limitation at page 7, line 7, page 33, lines 5-6, page 37, line 4 of the specification. The cited support has been considered but has not been found persuasive because a review of the cited support reveals support only for "ING2 activates p53 binding site controlled promoters in the presence or absence of p53" (p. 7, line 7), and support for "activate p53 binding site controlled promoters" (p. 33, lines 5-6), "activation of p53 binding site controlled promoters" (p. 37, line 3). It is noted that p34, line 4 is drawn to modulation of apoptosis, and/or modulation of cellular responses to stress. After careful review it is clear that none of the cited support is drawn to the broadly claimed limitation which now reads on both direct and indirect activation of a promoter having a p53 binding site. It is noted that the claims as currently constituted do not even require that the binding site be a consensus site that leads to the activation of the promoter

The cited support is drawn solely and specifically to proteins which activate p53 binding site controlled promoters. Although Applicant argues that the MPEP states that a claim amendment need not be *in haec verba*, this argument is not found persuasive because a review of MPEP 2163(I)(B) reveals clearly that while there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. It is clear that the newly added broad limitations are not supported by the specification expressly, implicitly or inherently since the teachings of the specification are clearly drawn to ING2 proteins that activate p53 binding site controlled promoters and not to the newly claimed recombinant ING2 proteins which increase activity of

a promoter having a p53 binding site. As drawn specifically to Claim 27 is it is clear that there is no teaching in the specification drawn to ING2 proteins that activate p53 binding site controlled promoters with at least 95% identity to SEQ ID NO:8. The subject matter claimed in claims 27, 30 and 32 broadens the scope of the invention as originally disclosed in the specification.

5. Claim 27 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 27 is drawn to a recombinant ING2 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell. Although drawn to the DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from ofher materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as □vertebrate insulin cDNA□ or □mammalian insulin cDNA□ without more, is not an adequate written description of the genus because it does not distinguish the genus from ofhers, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by

> members of the genus that distinguish them from ofhers. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that □naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, ofher physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, however, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of a recombinant ING2 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell, per Lilly by structurally describing a representative number of recombinant ING2 proteins comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete □by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe a recombinant ING2 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide any physical or chemical characteristics of a recombinant ING2 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding

site when introduced into a mammalian cell nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID Nos 2, 4, 6 and 8 which appear to have identical "p53 modulatory domain", this domain appears to lie somewhere within amino acids 30 to 229 of SEQ ID NO:8, however, there is no known or disclosed correlation between structure and function of increasing activity of a promoter having a p53 binding site, thus the teaching of the specification does not provide a description of a recombinant ING2 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell that would satisfy the standard set out in Enzo.

The specification also fails to describe a recombinant ING2 protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell by the test set out in Lilly. The specification describes several variants that contain only a single identical "p53 modulatory domain" that appears to lie somewhere within amino acids 20 to 229. Therefore, it necessarily fails to describe a representative number of the species composing the genus of amino acid sequences having at least 95% identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of a recombinant ING2 protein comprising an amino acid sequence having at least 95%

identity to SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell that is required to practice the claimed invention.

Applicant's arguments, submitted May 13, 2005, drawn to the previous written description rejection, are relevant to the instant rejection.

Applicant argues that the recent decision by the Board of Appeals and Interferences in the case of *Ex Parte Bandman,* wherein the claims recited "a sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:1" is relevant to the instant rejection. Applicant argues that the Board found that the claims were supported by the disclosure of a single representative species encompassed by the claims. Applicant attaches a copy of the decision as Exhibit A.

The argument has been considered but has not been found persuasive because a review of the Board decision revealed that although the claims are indeed drawn to a sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:1, and although the Board did decide that the recitation of a single sequence met the Written Description Guidelines for the genus of polypeptides claimed, the fact pattern of the *Ex Parte Bandman* and the instant application are very different. In the *Ex Parte Bandman* case, the claims are drawn to "naturally occurring amino acid sequences" wherein the court found that "through the process of natural selection, nature will have determined the appropriate amino acid sequences". In the instant application the claims are drawn to recombinant polypeptide, they are not drawn to "naturally occurring" amino acid sequences, as previously stated, there is no correlation made between structure and function, the specification does not teach the appropriate amino acid sequences

and for the reasons set forth above, the claim is appropriate rejected under 35 USC 112, first paragraph as lacking an adequate written description.

8. If Applicant were able to overcome the rejections above, Claim 27 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a recombinant ING2 protein comprising SEQ ID NO:8 does not reasonably provide enablement for a recombinant ING2 protein having at least 95% identity to the contiguous sequence set forth in SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to recombinant ING2 protein having at least 95% identity to the contiguous sequence set forth in SEQ ID NO:8 wherein said recombinant ING2 protein increases activity of a promoter having a p53 binding site when introduced into a mammalian cell wherein said ING2 proteins are variants of SEQ ID NO:8. The specification teaches that ING2 activates p53 binding site controlled promoters in the presence or absence of p53. The specification further teaches that variants fall into one or more of three classes, substitutional, insertional or deletional variants. The variants typically exhibit the same qualitative biological activity as the naturally occurring analogue, although variants can also be selected which have modified characteristics (p. 13, lines 11-24).

One cannot extrapolate the teaching of the specification to the scope of the claims because protein chemistry is probably one of the most unpredictable areas of biofechnology. Although the specification teaches that variants fall into one or

more of three classes, substitutional, insertional or deletional variants, the specification fails to provide sufficient guidance as to how to make the broadly claimed variants. In particular, Bowie et al, of record teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, of record who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al, of record who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Given that there is neither teaching nor guidance as

to which amino acid residues are critical to the claimed function, the effect of alteration of any of the amino acids in the putative "p53 modulating" region of about 200 amino acids on the functionality of the claimed protein cannot be predicted. Further, given that there is no teaching as to the targets to which the claimed proteins would be expected to bind in order to increase the activity of a promofor having a p53 binding site, one could not predict, based only on the single "p53 modulating" region disclosed which of the amino acid residues in the region are critical. Although, as previously set forth, the specification teaches general screening techniques to ascertain general activities, it is noted that the courts have found that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004).

Thus, one would not know how to predictably make the claimed polypeptides that would function as claimed. It appears that one is left only with random experimentation in order to make polypeptides to be screened for the claimed activity.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to make the claimed invention so that it would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. No claims allowed.

7. All ofher objections and rejections recited in the previous Office Action are hereby withdrawn.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 4, 2005